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EXAMINER	
EPPERSON, JON D	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 10/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/801,157	Applicant(s) JOSEL ET AL.	
File Copy	Examiner Jon D Epperson	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Please note: The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1639. Also please note the change in Examiner.

Status of the Application

1. The Response and/or Amendment filed July 22, 2002 (Paper No. 9) is acknowledged.

Status of the Claims

2. Claim 6 was amended. No claims were added or cancelled. Therefore, claims 1-8 are still pending.

Withdrawn Objections/Rejections

3. The following Objections/Rejections are withdrawn:

A. The objection to the disclosure is withdrawn in view of applicant's amendments (see Paper No. 6, paragraph 7).

B. The objection to claim 6 is withdrawn in view of applicant's amendments (see Papaer No. 6, paragraph 8).

C. The rejection over the phrase "reactive side groups" under 35 USC § 112, Second Paragraph is withdrawn (see Paper No. 6, paragraph 15, section D).

D. The rejection over the "coupling of multiple hapten molecules" under 35 USC § 112, Second Paragraph is withdrawn (see Paper No. 6, paragraph 15, section E).

E. The rejection over the groups binding "via primary amino groups or thiol groups" under 35 USC § 112, Second Paragraph is withdrawn (see Paper No. 6, paragraph 15, section F).

F. The rejection over the groups binding "acid-labile groups" under 35 USC § 112, Second Paragraph is withdrawn (see Paper No. 6, paragraph 15, section H).

G. The 35 USC 102(b) rejection with regard to DeLeys (WO 93/18054) is withdrawn (see Paper No. 6, paragraph 18).

4. All other rejections and/or rejections are maintained and the arguments (see arguments below).

Maintained Rejections (Written Description)
Claim Rejections - 35 USC § 112, First Paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1,2, and 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a written description rejection.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. Claim 1 recites the process of producing a conjugate that

consists of a polymeric peptidic carrier linked to a solid phase that can have branched monomeric units and marker groups. Claim 2 further recites the coupling of additional monomeric units via reactive side groups. Claim 8 summarizes this process. Applicants' claims are directed to conjugates that are defined in functional terms. The claims use generic terminology such as "hapten," "marker group," "solid phase binding group," "reactive side groups," and "predetermined positions." These terms are set forth in the instant disclosure but the definitions are relative, broad and/or completely open-ended.

There are n unknown number of conjugates that would fall within the claimed genus for the following reasons. Claims 1, 2 and 8 contain no structural information whatsoever on the "haptens" and "marker groups" or solid phase binding groups." The entities in question could encompass widely varying structures.

The instant specification discloses only conjugates containing amino acid carriers with luminescent metal chelate marker groups and small organic molecule haptens that are attached through reactive amino groups. Applicants' claimed scope represents only an invitation to experiment regarding other possible "haptens," marker groups," "solid phase binding groups" and "reactive side groups." The claimed scope encompasses nucleotides as the "polymeric carrier" which are also not sufficiently described in the instant specification. Thus the application fails to describe sufficient examples of conjugates that are within the scope of the presently claimed invention.

With respect to adequate disclosure of the scope of the presently claimed generic applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided

July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

Therefore it is deemed that the disclosure is neither representative of the claimed genus nor does it represent a substantial portion of the claimed genus. Moreover, the claimed genus encompasses members, which are yet to be prepared or envisioned. This further evidences that the structural features of the exemplified conjugates do not constitute support for the claimed genus or a substantial portion thereof.

Response to Arguments

7. Applicant's arguments filed July 22, 2002 have been fully considered (and are incorporated in their entirety herein by reference) but are not found persuasive. The examiner's rationale is set forth below.

8. Applicants argue that the functional language e.g., "hapten," "marker group," "solid-phase binding group," "reactive side groups," and "predetermined positions" would have been

"clear" to one of ordinary skill in the art "based on both the description in the specification and the well-established definitions of those terms" (see Paper No. 9, pages 4-6, wherein applicants provide numerous examples of terms and definitions) and, as a result, "inasmuch as all terminology recited in the claims is both described in the specification and would be well understood by those of ordinary skill in the art, ... that the claims [would] reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention."

9. The Examiner respectfully disagrees. The Examiner contends that applicants would not be in possession of the claimed invention EVEN IF assuming arguendo that the functional language disclosed in the claims e.g., "hapten", "marker group", "solid-phase binding group," "reactive side groups," and "predetermined positions" would have been "clear" to one of ordinary skill in the art (which they are not, see 35 USC § 112, second paragraph, rejections below).

10. The claims are drawn to a genus encompassing an "unknown" number of methods for producing an "unknown" number of conjugates and the genus is highly variant because there is no structural limitations placed on the component structures e.g., a "hapten," "marker group," "solid-phase binding group," "reactive side groups," and, as a result, there are no limitations placed on the methods used to produce those structures. Furthermore, the specification and claims do not indicate what distinguishing process steps are shared by the members of this genus. It would appear to the Examiner that the method steps would change in a "case-by-case" basis

depending on the structure of the conjugate that is produced, which is "unknown" in many cases (see next paragraph). In other words, applicants cannot be in possession of the claimed invention because they are not in possession of method steps for producing "unknown" compounds because applicants would not know what method steps would be required to make these "unknown" compounds. No common method steps are used to produce all or even a substantial portion of the members of this genus. The general knowledge and level of skill in the art do not supplement the omitted description because ***specific, not general, guidance is what is needed***. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

11. Many of the compounds disclosed by applicant are "unknown" because applicants use only functional language to describe the reactants and products e.g., "hapten", "marker groups", "solid phase binding groups" used and/or produced by the claimed invention. Consequently, no structural information is provided. Although conjugates that comprise peptidic backbones that have certain specific "hapten molecules" and "marker groups or solid phase binding groups" attached thereto via "reactive side groups" are known in the art at the time of filing, only a limited number of such conjugates were known in the art (see rejections below). Furthermore, the specification gives no guidance to permit one of skill in the art to determine what other compounds would fall within the broad scope of this functional language.

12. For example, what chemical "structures" would be encompassed by the term "hapten"? This question cannot be answered because "hapten" defines a product by its function i.e., its generation of an immunological response, not by its structure. Consequently, the Examiner contends that applicants did not know at the time of filing (and still do not know) ***all*** of the structures that are encompassed by this functional language e.g., all of the structures that are encompassed by the term "hapten". Consequently, applicants cannot know and hence cannot be in possession of all the methods that would be required to produce this limitless set of compounds. Furthermore, this problem is compounded by applicant's use of multiple functional terms e.g., "marker groups", "solid phase binding groups", "reactive side groups", since the specification and claims do not place any limit on the number of "marker groups", "solid phase binding groups" or "reactive side groups" either. Furthermore, applicants do not place any limitations on the way these compounds may be connected since it is to be determined in the future on a "case-by-case" basis (see Paper No. 9, page 7). Therefore, applicants could not be in possession of methods to produce these compounds at the time of filing since the structures of the compounds that they are trying to produce are going to be determined in the future on a "case-by-case" basis.

13. Applicant's arguments that the specification does provide some limitations on the structure of the functional language are not found persuasive. For example, the fact that the specification describes the phrase "marker group" to include "luminescent metal chelates" and "fluorescent labels" is not convincing because the specification does not specify what the phrase "marker group" does not include e.g., the phrase "marker group" could include "luminescent

metal chelates", "fluorescent labels" ***AND*** every other molecule known including molecules yet to be discovered. Furthermore, the terms "luminescent metal chelates" and "fluorescent labels" are also broad and ill-defined as it is not clear what structures would be encompassed by these terms. In addition, limitations have NOT been placed on much of the other functional language. For example, what restrictions have been placed on the structures of the molecules encompassed by the term "hapten"? The term "hapten" would literally read on any structure. In addition to applicant's argument, it is noted that the features upon which applicant relies (i.e., limitations in the specification and literature references) are **not** recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

14. "[T]he essential goal of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978). Another objective is to put the public in possession of what the applicant claims as the invention so that the public may ascertain if the patent applicant claims anything that is in common use, or already known. *Evans v. Eaton*, 20 U.S. (7 Wheat.) 356 (1822).

15. The Examiner's position is that the instant claims do not convey that the inventors were in possession of what is set forth in the claims. The rejection above is maintained because applicants disclose only a *limited number* of examples that do not provide adequate description for the many possible process steps that are encompassed by the broad functional language.

Therefore, it is deemed that the disclosure is neither representative of the claimed genus nor does it represent a substantial portion of the claimed genus. Moreover, the claimed genus encompasses members, which are yet to be prepared or envisioned. This further evidences that the structural features of the exemplified conjugates do not constitute support for the claimed genus or a substantial portion thereof. For these reasons, the above rejection under 35 USC 112, first paragraph is maintained.

Maintained Rejections (Enablement)
Claim Rejections - 35 USC § 112, First Paragraph

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a) conjugates where he polymeric carrier comprises amino acids as the monomeric units and (b) the use of a ruthenium bipyridine luminescent metal chelate marker group, does not reasonably provide enablement for (a) conjugates where the polymeric carrier comprises nucleotides or nucleotide analogues as the monomeric units or (b) marker groups other than ruthenium bipyridine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is clear from applicant's specification how one might practice this invention with specific polymeric carriers that comprise amino acids (or modified versions thereof); however, there is insufficient guidance as to how to make/use conjugates where the

polymeric carrier comprises nucleotides as the monomeric units. In addition, it is clear from the applicants' specification how one might practice this invention with a specific marker group that comprises a ruthenium bipyridine luminescent metal chelate; however, there is insufficient guidance as to how to make/use other marker groups that contain other metal centers and/or chelating groups. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: The claims are drawn to conjugates that comprise a polymeric carrier that is made up of monomer units that are amino acids (or modified versions thereof) or nucleotides. These conjugates further comprise 1-10 "hapten molecules" and 1-10 "marker groups" or "solid phase binding groups." These moieties are attached to the polymeric carrier via "reactive side groups" at "predetermined positions." Such represents very broad scope.

(3 and 5) The state of the prior art and the level of predictability in the art: The process of preparing conjugates that comprise peptidic backbones that have certain specific "hapten molecules" and "marker groups or solid phase binding groups" attached thereto via

"reactive side groups" are known in the art at the time of filing (see rejections below); however, only limited numbers of such conjugates were known and the specification gives no guidance to permit one of skill in the art to devise strategies for synthesis of conjugates with other types of backbones (i.e. sugar-phosphate backbone of DNA). The structures of possible variants are sufficiently diverse and one of ordinary skill would not be able to predict their structures.

(4) The level of one of ordinary skill: The level of skill would be high, most likely at the Ph.D. level. Such persons of ordinary skill in the art, given its unpredictability, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have provided an example of a conjugate containing an amino acid carrier (lysine derivative) with a luminescent ruthenium bipyridine metal chelate marker group and a small organic molecule hapten (which recognizes estradiol) that are attached through reactive amino side groups. Thus, the teachings of the instant specification coupled with the examples only support conjugates comprising specific polymeric carriers that comprise amino acids (or modified versions thereof), utilize a luminescent ruthenium bipyridine metal chelate marker, and utilize an estradiol hapten.

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: In claims 1-8, there is only a broad recitation that he claimed conjugates comprise a polymeric carrier that is made up of monomer units that are amino acids (or modified versions thereof) or nucleotides. These conjugates further comprise 1-

10 "hapten molecules" and 1-10 "marker groups or solid phase binding groups." These moieties are attached to the polymer carrier view "reactive side groups" at "predetermined positions." However, the instant specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in making and using he full scope of the claimed conjugates (i.e., when the polymeric carrier comprises nucleotides or the marker group is another compound besides ruthenium bipyridine). Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Response

18. Applicant's arguments filed July 22, 2002 have been fully considered (and are incorporated in their entirety herein by reference) but they were not found persuasive. The examiner's rationale is set forth below.

19. Applicants argue that the specification as filed provides one of ordinary skill in the art the wherewithal to practice the invention commensurate in scope with the present claims.

Applicants cite several examples of "polymeric carriers" and "marker groups" that have been set forth in the specification and literature along with "direction and guidance of a more general nature" that enable (according to applicants) one of ordinary skill in the art to make and use the claimed invention commensurate in scope with the present claims (see Paper No. 9, pages 6-7, wherein applicants provide several examples).

20. The examiner respectfully disagrees. The specific examples provided by applicant are not enough to enable one of ordinary skill in the art to make and use the invention as broadly as it is currently claimed. The functional language in the claims e.g., "hapten," "marker group," "solid phase binding group," "reactive side groups," and "predetermined positions." could read on a wide variety of structures that are not taught by the specification or the prior art. Consequently, it is the examiner's position that applicants have ***not*** provided methods of making and using the claimed invention that bears a "reasonable correlation to the entire scope of the claim" (MPEP 2164.01(b)).

21. The Examiner refers applicants to Riley *et al* for the sole purpose of providing a specific example to rebut applicants' arguments and affirm the argument on record that applicants are not enabled for the broad scope of the claimed invention. Riley *et al* discloses idiosyncratic hypersensitivity reactions (which may account for up to 25% of all adverse drug reactions) that are "unpredictable" in nature (see Riley et al, abstract). Riley et al states, "[t]he multifactorial nature of hypersensitivity reactions, particularly the role of often ***unidentified***, reactive drug metabolites [haptens] in antigen generation, has hampered the routine diagnosis of these

disorders" (see Riley et al, abstract). In other words, Riley *et al* specifically states that the identity and structure of many haptens associated with idiosyncratic hypersensitivity reactions have not be determined because these haptens represent metabolic intermeidates that are difficult to isolate for physical characterization. Where does the specification and/or prior art teach a person of ordinary skill in the art how to chemically link an "unidentified" hapten to a synthetic carrier? What specific chemical reactions should be used to attach the carrier to the "unidentified" functional groups of the haptens? What if these "unidentified" haptens don't have any functional groups at all? How would these haptens be attached to the carrier? Clearly, the specification is not enabled for ***all*** haptens.

19. The question at hand is whether applicant has taught how to ***make and use*** the full scope of the claimed invention. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention ***as broadly as it is claimed***. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991). The examiner's position is that the instant specification does not provide the necessary direction and guidance and the level of skill in the art was not such that a person of ordinary skill in the art would know how to make and use the invention as broadly as it is claimed. Also, see MPEP 2172.01

22. Furthermore, it is not possible to predict *a priori* whether haptens (e.g., haptens that could be identified and physically characterized) will retain their desired immunological properties when bound to a carrier. Will a hapten remain biologically active when bound to an oligomer

with 100 alanine residues? Will that same hapten remain biologically active when bound to an oligomer with 10 adenines? How would a person of ordinary skill in the art be able to predict *a priori* the effects of linking a hapten to a carrier? The specification does not provide "direction and guidance of a more general nature" that would solve this problem (see Paper No. 9, page 6).

23. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved. See *In re Fisher*, 57 CCPA 1099,427 F.2d 833,839,166 USPQ 18,24(1970). Additionally, the Board has held on the issue of unpredictability that "... the unpredictability of an art area alone may be enough to create a reasonable doubt as to the accuracy of statements in the specification." *Ex parte Singh*, 17 U.S.P.Q.2d 1714,1716 (B.P.A.I. 1990). The Examiner maintains that the invention encompasses art that is inherently unpredictable and, consequently, the specification does not provide enablement for the full scope of the claims.

24. In addition, the Examiner notes that applicants have not provided any examples of "marker groups" that include "alternatives to metal chelates" (see Paper No. 9, page 7, wherein applicants state in general terms that they are enabled for alternatives to metal chelates but provide not specific examples). Furthermore, applicants have not provided examples or "direction and guidance of a more general nature" for the other functional terms e.g., "solid phase binding group", "hapten" and "reactive side groups" at "predetermined positions". Based on the wide variety of chemical structures encompassed by the claimed moieties and the lack of

clear guidance in the specific structures and linkages thereof, the examiner deems that applicants are not enabled for the full scope of the claims.

20. Finally, please also note that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See *In re Budnick, 537 F.2d at 538, 190 USPQ at 424; In re Schulze*, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); and *In re Cole*, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant's attorney, the court indicated that factual affidavits could have provided important evidence on the issue of enablement. See *In re Knowlton*, 500 F.2d at 572, 183 USPQ at 37, and *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). Therefore the rejection is maintained for this reason and the reasons above.

Maintained Rejections

Claim Rejections - 35 USC § 112, second paragraph

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1 (step b), 2 (step b), 5 and 8 (step b) recite, "monomeric units covalently bound to marker groups or solid phase binding groups ..." It is not clear what the

applicants mean by the solid phase binding groups" since the amino, carboylate, or any nucleophilic groups of the monomeric units can bind to a solid support. It is unclear as to what is the structure of the binding groups and the nature of the "solid phase binding" interaction. Is the phrase "solid phase binding" meant to encompass any type of binding – covalent, non-covalent, etc? Is there a specific interaction between a solid phase binding group and a solid phase resin or are the groups merely functionalities that can bind to any solid phase? Applicants are requested to clarify.

Response

The rejection is maintained. Applicant's arguments filed July 22, 2002 have been fully considered (and are incorporated in their entirety herein by reference) but they were not found persuasive. It is still not clear what chemical groups would fall within the scope of "solid phase binding groups." For example, the Mayer and Neuenhofer reference does not address the issue of whether or not the "solid phase binding groups" would include groups for non-covalent attachment. Furthermore, it is not clear how one would differentiate a "solid phase" binding group from a "solution phase" binding group? What are some examples of chemical groups that are only "solution phase" binding groups and not "solid phase" binding groups? If there is no distinction, how does the term "solid phase" further limit the claim?

B. Claims 1, 2 and 8 (1 (step b), 2 (step b), and 8 (step b)) recite, "introducing the carrier at predetermined positions ..." It is not clear on what basis the applicant

determines such "predetermined" positions. Depending on the number of monomeric units in the conjugate, there are many possible positions and combination of positions to add further monomeric units to the conjugate. Applicants are requested to clarify.

Response

The rejection is maintained. Applicant's arguments filed July 22, 2002 have been fully considered (and are incorporated in their entirety herein by reference) but they were not found persuasive. Applicant argues that these "predetermined" positions should be "determined on a case by case basis" and that the "precise locations on the carrier are not restricted, but rather are chosen to coincide with desired points of attachment of haptens, marker groups, or solid phase binding groups to the carrier chain." The examiner contends that it is not clear what the "desired points of attachment" would be? What is the basis for determining the "desire" to attach at one place as opposed to another? Why wouldn't all possible points of attachment be desirable? If all possible points of attachment are desirable, how then does the term "predetermined" positions further limit the claims? Applicants cannot claim that a term is clear and concise when they define it with vague and imprecise terminology.

C. Claims 1, 2 and 8 (1(step b), 2 (step b), and 8(step c)) recite monomeric units consisting of "nucleotide analogues." It is not clear by what is meant by a nucleotide analogue, which can consist of multiple modifications to a nucleotide molecule, including glycosylation of the ribose ring, substituting phosphodiester

linkages with thiophosphodiester bonds and using peptide bonds (peptide nucleic acids) to link the nucleotides. Applicants are request to clarify.

Response

The rejection is maintained. Applicant's arguments filed July 22, 2002 have been fully considered (and are incorporated in their entirety herein by reference) but they were not found persuasive. Applicant argues that "nucleotide analogues" is "well understood" in the art and that they are structurally similar to other nucleotides apart from one "or more" structural differences. Applicant further argues that the phrase "nucleotide analogues" refers to carriers that retain their capacity to bind haptens, marker groups, and/or solid phase binding groups regardless of an such modifications to their nucleic structure." The examiner maintains that it is still not clear what compounds would be included in a subset of molecules that could have one "or more" structural differences from nucleotides. According to applicant a nucleotide with an infinite number of modifications (one ***or more***) would fit within this definition and could potentially include an infinite number of compounds. Conseqeuntly, it is not possible to determine the metes and bounds of the claimed invention. Furthermore, applicants argument that the compounds must be structurally similar to the nucleotides would also be rejected because the term "structurally similar" is a relative term and the degree of similarity is not defined. Finally, the Examiner argues that the prior art does not provide a standard definition for "nucleotide

analogue" and one of ordinary skill in the art would not know what the metes and bounds of this limitation was.

D. Claims 2 (step b), 6, and 8 (step b) recite "reactive side groups." It is unclear as to what is considered a reactive side group and where such groups are located. If the monomeric units are made up of amino acids, then there are some side groups of the 20 naturally occurring amino acids that are not considered reactive (i.e., glycine, alanine). If the carrier comprises nucleotide monomers, it is further unclear about the identity and location of the reactive side groups. Applicants are requested to clarify.

Response

The rejection is withdrawn.

E. Claims 2 (step d), 4, and 8 9step c) recite the "coupling of multiple hapten molecules" to the "reactive side groups." It is unclear as to the identity of the hapten molecules and how many are actually being coupled to the conjugate structure. Is it one type of hapten molecule, multiple types of the same hapten, or a combination of different haptens? Applicants are requested to clarify.

Response

The rejection is withdrawn.

F. Claim 5 recites that the monomeric groups are "bound via primary amino groups or thiol groups." It is unclear as to when and how primary amino groups or thiol groups are being used for binding. If peptide bonds are linking the monomeric units together, then primary amino groups and carboxyl groups are needed to

make the peptide bonds. If nucleotide analogues that contain thiol groups are used for linking the monomers, then the thiol groups would be used for binding. In addition, what types of groups, primary amino or thiol, are being used to bind the hapten molecules, marker groups and/or the solid phase binding groups to the monomeric units? Applicants are requested to clarify?

Response

The rejection is withdrawn.

G. Claim 6 recites "protective groups" that are "selectively cleavable." it is unclear as to when and how some protective groups are cleavable and when the protective groups are uncleavable. Selection of protective groups is based on reaction conditions and the specific reactivity of the protective groups. The specification does not clearly describe such reaction conditions. Applicants are requested to clarify.

Response

The rejection is maintained. Applicant's arguments filed July 22, 2002 have been fully considered (and are incorporated in their entirety herein by reference) but they were not found persuasive. Applicant argues that selectively cleavable protecting groups are well known in the art and the Examiner agrees to the extent that many books have been written that describe a large number of protecting groups. However, it would appear to the Examiner that all groups are selectively cleavable. In other words, all protecting groups will require some particular reagent to cleave them. In other words, no protecting group can be cleaved by all

reagents all the time under any conditions because that would defeat the purpose of a "protecting" group i.e., there has to be a certain amount of selectivity. Therefore, it is not clear to the Examiner how the word "selectively" further limits "cleavable." Furthermore, the term "selectivity" is a relative term. To what extent does one protecting group need to be cleaved in the presence of a particular reagent to be regarded as "selectively" cleavable? Would a protecting group that cannot be cleaved at room temperature with acid be considered selectively cleavable if it could be cleaved at 10,000 degrees Celsius with the same amount of acid? What are the conditions for the outer limits? Consequently, it is not possible to determine the metes and bounds of the claimed invention.

H. In claim 7, it is unclear as to what is meant by "acid-labile groups" and "acid-stable groups." Acid lability and stability varies depending on the particular protective group moiety being used. Applicants are requested to clarify.

Response

The rejection is withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 102

25. Claims 1-8 are rejected under 35 USC 102(b) as being anticipated by EP0155224 (Crockford, March 14, 1985) 9reference #11 from the IDS provide by applicant in PTO-1449 filed on 12/4/2001).

Claims 1, 3 and 8 recites the process of producing a conjugate that consists of polymeric peptidic carrier linked to a solid phase that can have branched monomeric units and marker groups. claim 8 summarizes this process. Claims 5-7 recites the types of reactive groups used in binding marker and solid-phase binding groups (claim 5), the cleavability of the protective groups (claim 6) and the selection of a protective group based on reactivity in the production of the conjugate complex (claim 7).

Crockford discloses "a method for preparing a reagent which is useful in the determination of one component of an antibody-antigen characterized by: (a) covalently linking an antibody to a solid support matrix; (b) separately forming a conjugate with a carrier molecule of said antigen and a chromagenically-responsive marker; and 9c) reacting said antibody-modified solid support matrix with said conjugate" (see reference claims 15-24). The reference claims 15-24 refer to the instant claims 1, 3 and 8. The reference discloses, "said conjgate contains one or two molecules of antigen (refers to hapten of instant claims) and between about 4 and 15 molecules of marker per carrier molecule" (see reference claim 23). In this disclosure, the antibody-modified solid support matrix is the carrier (refers to instant claim 1, step a). The carrier disclosed in the reference is attached to the antibody-modified solid support matrix. Since an antibody is made up of amino acids, it satisfies the "monomer unit" requirement of the instant invention (refers to instant claims 1, step b and 3). Additionally, since the antibody is attached to the solid support matrix, the carrier contains monomeric units that are covalently bound to solid phase binding groups (refers to instant claim 1, step b). The reference antigen (hapten) is human chorionic gonadotropin (see reference claim 24). Pages 12-16 of the reference give four examples of preparing various conjugates.

In addition, the reference discloses the role of primary amino groups in the chemical reactions (instant claims 5-6) and protecting groups were used in synthesizing the conjugates (instant claim 7); Example 2 (p.13, lines 23-26) discloses the "amino groups on the surface of the hCG molecule were extensively maleimidated with MCS." The MCS was used to protect the amino groups in the reference invention. The reference clearly anticipates the claimed invention.

Response

26. The rejection is maintained. Applicant's arguments filed July 22, 2002 have been fully considered (and are incorporated in their entirety herein by reference) but they were not found persuasive. The Examiner's rationale is set forth below.

Applicants argue that "Crockford was cited in the International Search Report as a cetegory "A" reference" implying that it is only a general reference and not to be used as prior art. The Examiner contends that the USPTO is not bound by the categories cited in the International Search Report and, as a result, the argument is moot.

Applicants further argue that the description of he carrier molecules in Crockford is limited to sucrose polymers (e.g., Ficoll70) and bovine serum albumin and thus does not fit into the group consisting of nucleotides, nucleotide analogues and amino acids. The Examiner respectfully disagrees. As stated above in the 35 USC 112, second paragraph rejection above, it is not clear what is encompassed by "nucleotide analogue". Consequently, the Examiner has interpreted "nucleotide analogue" to include sucrose polymers. The fact that both are chains of monomers that contain carbocyclic rings linked together by covalent bonds provides the basis for

their similarity and thus one could be an "analogue" of the other. Therefore, the rejection is maintained (see also 35 USC 112, second paragraph rejection, part c).

27. Claims 1-4, 7 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 93/18054 (Deleys, September 16, 1993) (reference #21 from the IDS provided by applicant in PTO-1449 filed on 12/4/2001).

DeLeys discloses in claim 1, "(a) preparing peptides corresponding to portions of the amino acid sequence of the protein or polypeptide to be analyzed wherein said peptides are either contiguous or preferably overlapping by at least 3 amino acids; (b) biotinylation of said peptides; (c) binding said biotinylated peptides to a solid phase by interaction if the biotinylated group and streptavidin or avidin; and (d) measuring antibodies which bind to the individual peptides." The polypeptide chain of reference claim 1(a0 represents the carrier molecule. The peptides also represent the hapten groups since the antibodies of reference claim 1(d) bind to the individual peptides. The reference claim 1 refers to the to the instant claims 1 and 8. The instant claims 1 and 8 are interpreted as the process of producing a conjugate that has either a marker group or solid phase binding group attached to the carrier (In the instant claims it is not necessary to have a marker group attached to the carrier since the instant claim 19b) teaches that '1-10 additional monomeric units covalently bound to marker groups or solid phase binding groups ..."). Since the reference claims that the peptide binds to the solid phase binding groups..."). Since the reference claims that the peptide binds to the solid phase, the requirements of the instant claim 1(b) is met. The reference in page 22 (part 7, second

paragraph) further describes the process of preparing the peptide conjugates in which "the synthesis of the peptides may be achieved in solution or on a solid support" (refers to instant claims 1, step a and 8, step a). In addition, the reference discloses in page 23 "the use of biotinylated peptides, in the process of invention, makes the anchorage of peptides to a solid support such that it leaves their essential amino acids free to be recognized by antibodies" (references to the "solid phase binding groups" in instant claims1, step b and 8, step b). The reference in page 23, paragraph 3 also discloses, "the expression anchoring peptide to a solid support means the attachment of the peptide to a support via covalent bonds or non-covalent interactions such that the peptide becomes immobilized" (refers to instant claims 1, step b and 8, step b). Finally, the reference discloses the process of using an Fmoc protecting group on the peptide in claims 16-22 (refers to the use of a protective group in instant claim 7). The reference clearly anticipates the claimed invention.

Response

28. The rejection is withdrawn.

29. Claims 1, 3 and 5-8 are rejected under 35 USC 102(b) as being anticipated by Tam (US patent # 5,229,490, July 20, 1993).

Claims 1, 3 and 8 recites the process of producing a conjugate that consists of a polymeric peptidic carrier linked to a solid phase that can have branched monomeric units and marker groups. Claim 8 summarizes this process. Claims 5-7 recites the types of reactive groups used in binding marker and solid-phase binding groups (claim 5), the cleavability of the

protective groups (claim 6) and the selection of a protective group based on reactivity in the production of the conjugate complex (claim 7).

Tam discloses his invention in columns 4 and 5, stating that, "the invention ... provides a multiple antigen peptide system comprising a dendritic polymer base with a plurality of anchoring sites covalently bound to anitgenic molecules. The antigenic molecules are principally described herein as peptide antigens ... The selected antigen may be ... joined to the carrier. Alternatively, the antigen may be synthesized on the carrier." In addition, Example 1 in columns 11 and 12 teach that, The synthesis of a octabranched matrix core with peptide antigen was caried out manually be a stepwise solid-phase procedure on Boc-βAla-OCH_2-Pam resin ..." Example 2 in columns 12 and 13 gives a detailed "Synthesis and Purification of (Asn-Ala-Asn-Pro)$_8$-MAP(NP-16MAP)." Tam discloses a "conjugate" that is "formed on a solid phase by linking together monomeric unties" (refers to instant claim 1, step a, and claim 8, step a), has definite "predetermined positions" on which to introduce additional monomeric unites (referst to instant clams 1 step b, 8 step b), is covalently bound to a "solid phase" (referes to instant claim 1, steps a & b, and claim 8, steps a & b), and the conjugate of the reference meets the requirement for "comprising a maximum of 100 monomeric units selected from the group consisting of ... amino acids" (refers to instant claim 1, step b, claim 3, and claim 8 step c).

In addition, the reference discloses, "the introduction into the carrier at predetermined positions additional monomeric units comprising reactive side groups and protecting groups for said side groups" (refers to instant claim 8, step c) and "cleaving said protecting groups" (refers to instant claim 7, and claim 8, step c) in Example 1, columns 11 and 12. According to Tam, the monomeric units do not have to be just amino acids as stated in instant claim 1, step b, claim3

and claim 8, step c. According to column 10, lines 34-39, Tam discloses, "Additionally, the core molecule could support a structure other than a polyamide, and the antigen need not necessarily be a peptide. The covalent bond which joins the antigen or other supported moiety to the carrier may be an ester, ether, urethane or some other type of covalent linkage." The instant claim 1, step b and claim 8, step c discloses, "monomeric units selected from the group consisting of nucleotides, nucleotide analogues and amino acids." Since the instant claims 1 step b and claim 8 step b teach, "1-10 additional monomeric units covalently bound to marker groups or solid phase binding groups," Tam clearly anticipates the claimed invention. Tam discloses in column 5, lines 5-7, "the available functional groups on the polymer are amino groups or carboxyl groups,' (refers to the instant claims 5 and 6) and teaches in column 8, lines 11-14, "molecule employing different amino blocking groups, one of which is stable to acid hydrolysis, the other which is stable to alkaline hydrolysis" (refers to the instant claim 7). The reference clearly anticipates the claimed invention.

The instant invention recites the use of marker groups conjugated to monomers. Tam discloses in column 10, lines 40-55, "The products of the invention may be employed in various diagnostic tests, including radioimmunoassay, precipitation, complement fixation, direct and indirect immunofluorescence, agglutination and enzyme linked immunoassay. For such testing the diagnostic moiety joined to the dendritic polymer may be labeled with a detectable label, or it may be caused to react with a labeled product such as a labeled antibody to product a detectable reaction product. Useful labels include fluorescent labels such as fluorescein, rhodamine or auramine ...," which refers to using marker groups as recited in the instant claim 1, step b and claim 8, step b.

Response

30. The rejection is maintained. Applicant's arguments filed July 22, 2002 have been fully considered (and are incorporated in their entirety herein by reference) but they were not found persuasive. The Examiner's rationale is set forth below.

Applicants argue that Tam does not teach or suggest introducing into carriers "monomeric units covalently bound to hapten molecules and ... monomeric units covalently bound to marker groups or solid phase binding groups", nor does it teach or suggest introducing into carriers "monomeric units comprising reactive side groups and coupling hapten molecules and marker groups or solid phase binding groups thereto" (see Paper No. 9, page 10, second to last paragraph).

The Examiner respectfully disagrees. Tam does teach "monomeric units covalently bound to hapten molecules and ... monomeric units covalently bound to marker groups or solid phase binding groups." As stated in the previous office action, the dendrimer can be regarded as a carrier and the attached peptide antigens can be regarded as hapten molecules (see Tam et al, Figure 1, showing Peptide antigen [haptens] linked to lysine dendritic [carrier] wedge via glycine linkers). Furthermore, Tam clearly recites the use of marker groups conjugated to monomers. and discloses in column 10, lines 40-55, "The products of the invention may be employed in ... direct and indirect immunofluorescence ... [wherein] the diagnostic moiety joined to the dendritic polymer may be labeled with a detectable label ... useful labels include fluorescent labels such as fluorescein, rhodamine or auramine." (see Tam et al, column 10, lines 40-55).

Applicant's argument that the marker groups are not taught with the carrier and the hapten because "there is no teaching as to how such labels should be attached to the dendritic

polymers, nor indeed at what positions they should be attached" is not found persuassive. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "how such labels should be attached" and "at what positions they should be attached") are not recited in the rejected claim(s). The claims simply do not address the issue of "how" the labels are to be attached to the carrier. Furthermore, the position at which the labels should be attached is also not addressed by the claims because the "predetermined" locations of the monomers that covalently bind to the marker groups are vague and indefinite (see 35 USC 112, Second Paragraph Rejection above). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In addition, the claims states that the "1-10 additional monomeric units can be covalently bound to "marker groups OR solid phase binding groups" i.e., marker groups are not even required. Clearly, the peptide antigen linked dendrimer contains a "solid phase binding group" since it was cleaved from a solid phase resin (see Tam et al, Example 2). Therefore, the claims would still be anticipated even if it could be shown that the "marker groups" were not anticipated (see also Tam et al, Figure 1, wherein the Gly-OH could be bound to a solid phase resin).

Applicants further argued that Tam does not "teach or suggest introducing into carriers "monomeric units comprising reactive side groups" and coupling hapten molecule and marker groups or solid phase binding groups thereto, as called for by independent claim 2." Again, the Examiner respectfully disagrees. As pointed out in the previous office action, Tam et al does teach the concept of introducing into carriers [i.e., dendrimers] monomeric units comprising

reactive side groups (see Tam et al, column 5, lines 5-7, which reads on reactive side groups in the polymer i.e., amino and carboxyl groups) ("the available functional groups on the polymer are amino groups or carboxyl groups"). As for introducing "haptens" and "marker groups" or "solid phase binding groups", the arguments in the preceding paragraphs would also apply equally here. Therefore, Tam et al does anticipate the claimed invention and, as a result, rejection is maintained.

Status of Claims/Conclusion

31. No claims are allowed.

32. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

41. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D. Epperson, Ph.D. whose telephone number is (703) 308-2423. The examiner can normally be reached on Monday-Thursday from 9:30 to 7:00 and alternate Fridays.

42. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Jon D. Epperson, Ph.D.
October 11, 2002

BENNETT CELSA
PRIMARY EXAMINER